Remarks

Applicant respectfully requests reconsideration.

The specification and claims are amended to correct a typographical error by replacing the recitation of "antigen dependent cell cytotoxicity" with "antibody dependent cell cytotoxicity". Support for this amendment can be found in the specification on page 49 line 31 through to page 50 line 7.

Claims 6, 7, 17 and 18 are now cancelled.

Claims 1, 2, 19, 20, 46 and 96 are amended. Claim 1 has been amended to recite a nucleotide backbone comprising at least one phosphorothioate modification. Support for this amendment can be found at least in originally filed claims 1, 17 and 18, and in the specification on page 4 lines 5-7. Claims 1, 2, and 46 have been amended to refer to "immunostimulatory nucleic acid" rather than "immunostimulatory nucleic acid molecule" for the sake of consistency. Claims 19 and 20 are amended to depend from pending claim 1. Claim 96 has been amended to correct a typographical error by replacing "antigen dependent cellular toxicity" with "antibody dependent cellular toxicity". Support for this amendment can be found in the specification at least on page 49 line 31 to page 50 line 7.

New claims 100, 101 and 102 have been added. Support for new claim 100 can be found in the specification at least on page 10 lines 24-25. Support for new claim 101 can be found at least in originally filed claims 1 and 3. Support for new claim 102 can be found in the specification at least on page 14 line 13.

No new matter has been added.

Claims 1-5, 8-15, 19-21, 23, 28-33, 44, 46-58, 64-66, 71-74, 77-81, 84, 85, 89, 90, 95, 96, 98 and 100-102 are pending, with claims 1 and 100-102 being independent claims. Claims 5, 13, 15, 46-58, 64-66, 71-74, 77-81, 84, 85, 89, 90, 95, 96 and 98 are currently withdrawn. Claims 1-4, 8-12, 14, 19-21, 23, 28-33 and 44 are under consideration.

Restriction/Election

Applicant acknowledges that Group III claims will be rejoined with Group I claims, once the latter are deemed allowable.

Double Patenting Rejection

Claims 1, 3, 8-10, 17, 18, 20, 21, 23 and 30-33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 41-46, 52-56 and 58 of co-pending Application No. 10/816,220 (2004/0076905).

Without conceding the Examiner's position, Applicant defers substantive rebuttal until the cited claims are allowed.

Rejection under 35 U.S.C. §112

Claims 1-4, 8-12, 14, 17-21, 23, 28-33 and 44 are rejected under 35 U.S.C. §112, first paragraph, enablement. The Examiner acknowledges that the specification is "enabling for a composition comprising SEQ ID NO:1 and an antigen (HbsAg) and its use". However, the Examiner states that the specification "does not reasonably provide enablement for a composition comprising SEQ ID NO:1, a cancer antigen and chemotherapeutic agent and the use of the composition." The Examiner states that the "use of the composition would be for treatment in cancer in view of the descriptions in the specification" and that such use is not enabled. Applicant respectfully traverses for the reasons set forth below.

At the outset, Applicant stresses that the claimed invention is a composition, and as such is not limited by a recited use. MPEP 2164.01(c) sets forth that "when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use". The MPEP further states that "if any use is enabled when multiple uses are disclosed, then the application is enabling for the claimed invention". (Id.) As discussed herein, Applicant has demonstrated that the claimed composition induces immune responses *in vivo* and *in vitro*. Applicant has further demonstrated that the claimed composition induces innate and antigen-specific immune responses. Applicant has therefore shown how to use the claimed composition by way of examples that correlate with the entire scope of the claimed composition. MPEP 2164.01(c). Applicant is not required to demonstrate treatment or prevention of cancer as the claimed invention is not so limited. If the Examiner is suggesting that the addition of another agent to the nucleic acid (e.g. a chemotherapeutic agent) interferes with immunostimulation, she is required to support that position, particularly in view of the cited art discussed herein.

Applicant further traverses the rejection based on the following analysis. The enablement requirement is satisfied if one of ordinary skill in the art is able to make and use the claimed invention without undue experimentation, based on the specification and the knowledge in the art at the time of filing. The experimentation required to make and use the claimed invention may be complex, and still not undue, if the art routinely engages in that level of experimentation. The factors to be considered in determining whether undue experimentation is required include 1) the nature of the invention; 2) the breadth of the claims; 3) the state of the art; 4) the level of ordinary skill in the art; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor(s); 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality with no one factor being dispositive. The analysis of these factors as presented below illustrates that the experimentation required to practice the invention is not undue.

Nature of the invention: The invention relates to nucleic acids that comprise a defined nucleotide sequence (i.e., SEQ ID NO:1). These nucleic acids are, by definition, immunostimulatory.

Breadth of the claims: The claimed invention is a *composition* comprising a nucleic acid comprising at least a defined nucleotide sequence (i.e., SEQ ID NO:1). The composition may further comprise other elements such as antigens, adjuvants, and other disease-specific agents. The claimed compositions can be used to stimulate immune responses but they are not limited to any particular *in vitro* or *in vivo* use. Thus they can be used therapeutically or non-therapeutically.

State of the art: The state of the art at the time of filing was aware of immunostimulatory nucleic acids, including CpG immunostimulatory nucleic acids. The immunostimulatory properties of a number of CpG immunostimulatory nucleic acids were also known in the art at that time. (See, for example, USPs 6,194,388 and 6,207,646, issued prior to the effective filing date of the instant application and disclosing the ability of immunostimulatory nucleic acids to stimulate innate and antigen-specific immune responses.) The art therefore was familiar with how to make nucleic acids (including those comprising a defined nucleotide sequence) and how to use such nucleic acids to stimulate immune responses *in vitro* or *in vivo*.

Level of ordinary skill in the art: One of ordinary skill in the art would be able to make and use the claimed nucleic acids based on the level of ordinary skill. Such a person would be familiar with nucleic acid synthesis and ways of contacting immune cells with nucleic acids either *in vitro* or *in vivo*.

Level of predictability in the art: As stated above, the art was familiar with the existence of CpG containing nucleic acids capable of immunostimulation, and therefore the ability to make and use CpG containing nucleic acids for immunostimulation *in vitro* or *in vivo* would not be considered unpredictable. The Examiner however states that the state of the art of cancer therapy and the use of CpG nucleic acid in such therapy are unpredictable. Respectfully, the claimed invention is a *composition*; treatment of cancer is not a limitation of the claimed invention. The Examiner has put forth an enablement standard for the claimed composition in excess of what the law requires. Notwithstanding this, however, Applicant points out that CpG nucleic acids have therapeutic utility in the treatment of cancers as evidenced by the references cited in Appendix A and in particular USP 6,653,292 which is specifically directed to the use of CpG nucleic acids in the treatment of cancer.

The Examiner cites a number of references as evidence of the unpredictability in the cancer therapy and CpG nucleic acid arts. Applicant addresses each of these reference teachings below. Some of the references, e.g., Donnelly (*Nature Medicine* (2003) **9**(11):1354-1356), DeGruijl *et al.* (*Nature Medicine* (1999) **5**(10):1124-1125) and Bitton *et al.* (*Current Opinion in Molecular Therapeutics* (2004) **6**(1):17-25), are cited as evidence of the unpredictability of cancer vaccines. The Examiner is respectfully reminded that the claimed nucleic acids are capable of stimulating innate immune responses in addition to antigen-specific immune responses. The use of the these nucleic acids is therefore not limited to a vaccine setting. However, even when used with an antigen (e.g., a viral antigen), the claimed nucleic acids have adjuvant effects, as acknowledged by the Examiner. The Examiner provides no rationale for why such demonstrated adjuvant activity in the context of a viral antigen is not correlative of adjuvant activity in the context of a cancer antigen.

Donnelly is further cited for the teaching that "immunotherapy has yet to be incorporated into first-line therapies for more than a few types of cancers." However, Donnelly also states that "significant progress is being made, reflected in the number of successful phase 1 and 2 clinical trials." Indeed, the reference details the successful use of a vaccine together with all-

trans retinoic acid (an anti-cancer agent) in the treatment of acute promyelocytic leukemia, and concludes that "synergy between the immunotherapy and conventional chemotherapy" was shown. Moreover, the reference further states that vaccines used in combination with cytokines have been more successful than vaccines used alone. To this end, Applicant points out that the claimed nucleic acids stimulate cytokines, as documented on page 90 line 11 through to page 91 line 2. Accordingly, the teachings of Donnelly, when taken as a whole, support rather than refute enablement of the claimed invention.

DeGruijl *et al.* is further cited for the teaching that although "a variety of anti-tumor vaccine clinical trials have been undertaken ... there has been little evidence of clinical efficacy." However, the point of the reference is improvements in cancer vaccine strategies over pre-1999 strategies. For example, the reference describes a clinical trial by Bendandi *et al.* as making a "large advance over previous tumor vaccines" and having "benefited from the advances made in our understanding of anti-tumor immunity." The filing date of the claimed invention is after the DeGruijl *et al.* reference and accordingly the claimed invention must be viewed with light of the "large advances" made in anti-tumor immunity, including anti-tumor vaccines, which are supportive of immunotherapy in the treatment of cancer.

Bitton *et al.* is cited for the teaching that therapeutic vaccines have little use in cancer treatment. However, Bitton *et al.* documents successful vaccines, such as human papillomavirus (HPV)-16 vaccine and hepatitis B virus (HBV) vaccine (see page 18, left column, third paragraph). Importantly, the role of immunostimulatory nucleic acids, such as those currently claimed, in cancer vaccines is not contemplated in this review.

Some of the references cited by the Examiner are intended to support unpredictability in the CpG nucleic acid art. For example, Weiner *et al.* is cited (*J. Leukocyte Biology* (2000) **68**:455-463) for the teachings that there is a lack of understanding of the mechanism behind the immunostimulatory effects of CpG ODN, that not all CpG ODN are alike, and that heterogeneous responses are possible depending on sequence, host and cell subset. The Examiner's reasons for citing Weiner *et al.* however appear inapplicable to the claimed invention and the instant specification for a number of reasons. First, understanding mechanism is not a prerequisite to patentability. Second, the claimed invention does not relate to *any* CpG ODN, but rather a family of ODN having at least a 24 nucleotide consensus sequence (i.e., SEQ ID NO:1) to which immunostimulatory activity is attributed. And third, the instant Examples show that the

claimed nucleic acids stimulate mouse and human immune cells including B and NK cells, both of which are important in an anti-cancer response, as documented by Weiner *et al.*

Weiner *et al.* summarizes the immunostimulatory activity of CpG nucleic acids, and therefore actually argues for, rather than against, predictability in the CpG nucleic acid art. Weiner *et al.* disclose that CpG ODNs induce cytokines and activate immune cell subpopulations involved in anti-tumor immunity (page 460, right column, second paragraph). The claimed nucleic acids, including CpG ODN 10102, possess similar immunostimulatory profiles as those described by Weiner *et al.*, including B and NK cell activation, antibody secretion, IP-10 and IL-10 production, and IFN- α secretion. Moreover, according to Weiner *et al.*, there is a correlation between the *in vitro* and *in vivo* immunostimulatory effects observed with CpG nucleic acids (see page 457, right column, third paragraph). The reference further discloses that CpG nucleic acids induce an antigen-specific antibody response and protection against subsequent tumor challenge in a murine tumor model (see page 458, right column, last paragraph). When taken as a whole, therefore, the reference supports predictability of immunostimulation using CpG nucleic acids, including in a cancer therapy.

Krieg *et al.* (*Pharmacology and Therapeutics* (1999) 84:113-120) is cited for the teaching that although "CpG has NK-stimulating properties ... many or even most types of tumors are relatively resistant to NK-mediated lysis." Applicant points out that NK cell activation is but one element of the immune response induced by CpG nucleic acids, and that other elements of that response are also useful in anti-tumor immunity (e.g., B cell activation and cytokine induction). The reference discloses that activation of NK cells with CpG nucleic acids prior to treatment with monoclonal antibody enhances their efficacy in anti-cancer treatment (see page 117, right column, last paragraph). Even for tumors resistant to NK-mediated lysis, treatment with tumor-specific monoclonal antibodies and CpG nucleic acids was successful. The reference therefore does not stand for the proposition that CpG nucleic acids are ineffective in tumor immunotherapy.

Ballas *et al.* (*J. Immunology* (2001) 167:4878-4886) is cited for the teaching that a single CpG ODN cannot be used to treat all cancers and tumors. However, the Examiner acknowledges that Ballas *et al.* teaches that "CpG motifs can be custom-tailored for each desired immune effect" and that some CpG nucleic acids activate NK cells and are effective as a sole therapeutic agent at preventing the development of B16 melanoma. The reference demonstrates that mice

injected with B16 tumor have increased survival when treated with CpG ODN (see page 4880, left column). The reference concludes that rejection of the B16 tumor was due to the ability of CpG ODN to augment the killing activity of NK cells (see page 4882, right column). Applicant points out that CpG ODN 10102 demonstrates an immune response profile similar to that of CpG 7909, a CpG nucleic acid with demonstrated anti-cancer effects (see Appendix A).

Agrawal *et al.* (*Trends in Molecular Medicine* (2002) 8(3):114-120) is cited for the teaching that different effects are observed with different CpG nucleic acids. Applicant again respectfully reminds the Examiner that the claimed invention relates to a family of CpG oligonucleotides that share a 24 nucleotide consensus sequence, and not just *any* CpG ODN. The effects of this consensus sequence *in vitro* and *in vivo* have been demonstrated in the specification.

In summary, the cited art teaches that cancer vaccines have been successful and that CpG nucleic acids have immunostimulatory activities *in vitro* and *in vivo* that correlate with anti-cancer activity. The claimed nucleic acids possess an immune response profile comprising elements useful in anti-cancer therapy. Accordingly, the cited art, as a whole, supports rather than refutes the predictability of CpG nucleic acids in anti-cancer therapies.

Amount of direction provided by the inventor(s): Applicant teaches how to make the invention. The nucleotide sequence of SEQ ID NO:1 is provided. The art was familiar with how to make oligonucleotides of defined or random sequence and of particular backbone composition. In addition, the specification teaches *de novo* synthesis of nucleic acids using any number of procedures. (See page 21 line 16.) The specification also provides detailed instructions for introducing modifications into an oligonucleotide. (See pages 15-21.) The combination of an oligonucleotide and another agent such as an antigen, an adjuvant, an anti-cancer agent, and the like, would also be clear based at least on the teaching in the specification of examples of each category of agent to be combined with the claimed nucleic acids. A person of ordinary skill in the art would know how to make such combinations.

Applicant teaches how to use the invention. The ability of a number of CpG nucleic acids to stimulate immune responses was known at the time of filing. The specification teaches how to use the nucleic acids *in vitro* and *in vivo*. For *in vivo* use, the specification further teaches how to formulate, dose and administer the nucleic acids, and to whom to administer the nucleic acids. (See pages 81–88.) One of ordinary skill in the art would know how to determine if

immunostimulation has occurred in a subject based on the teaching of the specification and the knowledge and skill in the art at the time of filing.

Working examples: The Examples on pages 85-90 further demonstrate the use of SEQ ID NO:1 to elicit an immune response both *in vitro* and *in vivo*. For example, CpG ODN 10102 produces an immunostimulatory response that includes B cell activation and antibody secretion, and IP-10, IL-10 and IFN- α induction, and NK cell activation. CpG ODN 10102 also induces an antigen-specific immune response when administered with HbsAg to mice, as acknowledged by the Examiner. As stated in Weiner *et al.* many of the immunostimulatory activities induced by CpG ODN 10102 have been implicated in anti-cancer therapy.

Quantity of experimentation needed to practice the invention: In view of the teaching of the instant application and the state of the art at the time of filing, Applicant submits that the claimed invention can be practiced without undue experimentation. Applicant has identified the nucleotide sequence that confers immunostimulatory capacity on a nucleic acid and has taught how to use that nucleic acid to stimulate immune responses *in vitro* and *in vivo*.

In view of the foregoing, the specification enables the invention as claimed (i.e., a composition comprising a nucleic acid comprising SEQ ID NO:1). Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. §102

Claims 1 and 23 are rejected under 35 U.S.C. §102(a) as being anticipated by Olek *et al.* (WO 2002/18632 or WO 2001/92565). Claim 1 is amended to recite that the immunostimulatory nucleic acid has a nucleotide backbone comprising at least one phosphorothioate modification. Olek *et al.* does not teach phosphorothioate backbone modification of its nucleic acid sequences. Amended claim 1 finds its basis at least in originally filed claims 17 and 18 where were not rejected in view of Olek *et al.* New claims 100-102 also are not anticipated by Olek *et al.* New claim 101 finds its basis at least in originally filed claim 3 which was not rejected in view of Olek *et al.* The nucleic acids of claims 100 and 102 are not taught by Olek *et al.*

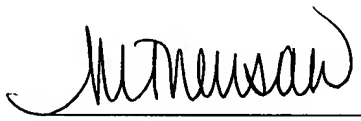
Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

If the Examiner has any questions and believes that a telephone conference with Applicant's representative would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 646-8266.

Respectfully submitted,



Maria A. Trevisan, Reg. No. 48,207
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: C1037.70041US00
Date: October 11, 2005
x10/09/05x

Appendix A

1: Proc Natl Acad Sci U S A. 1997 Sep 30;94(20):10833-7.

Immunostimulatory oligodeoxynucleotides containing the CpG motif are effective as immune adjuvants in tumor antigen immunization.

Weiner GJ, Liu HM, Wooldridge JE, Dahle CE, Krieg AM.

Department of Internal Medicine, University of Iowa, University of Iowa Cancer Center, University of Iowa Graduate Program in Immunology, and Iowa City Veterans Affairs Medical Center, Iowa City, IA 52242, USA.
george-weiner@uiowa.edu

Recent advances in our understanding of the immune response are allowing for the logical design of new approaches to cancer immunization. One area of interest is the development of new immune adjuvants. Immunostimulatory oligodeoxynucleotides containing the CpG motif (CpG ODN) can induce production of a wide variety of cytokines and activate B cells, monocytes, dendritic cells, and NK cells. Using the 38C13 B cell lymphoma model, we assessed whether CpG ODN can function as immune adjuvants in tumor antigen immunization. The idiotype served as the tumor antigen. Select CpG ODN were as effective as complete Freund's adjuvant at inducing an antigen-specific antibody response but were associated with less toxicity. These CpG ODN induced a higher titer of antigen-specific IgG2a than did complete Freund's adjuvant, suggesting an enhanced TH1 response. Mice immunized with CpG ODN as an adjuvant were protected from tumor challenge to a degree similar to that seen in mice immunized with complete Freund's adjuvant. We conclude that CpG ODN are effective as immune adjuvants and are attractive as part of a tumor immunization strategy.

PMID: 9380720 [PubMed - indexed for MEDLINE]

1: Cancer Res. 1999 Nov 1;59(21):5429-32.

Oligodeoxynucleotides containing CpG motifs can induce rejection of a neuroblastoma in mice.

Carpentier AF, Chen L, Maltonti F, Delattre JY.

Federation de neurologie Mazarin et INSERM U 495, Hopital de la Pitie-Salpetriere, Paris, France.

Phosphorothioate oligodeoxynucleotides with CpG motifs (CpG-ODNs) activate various immune cell subsets and induce production of numerous cytokines. To evaluate whether CpG-ODNs can induce rejection of established malignant tumor, A/J mice were challenged by the s.c. implantation of a syngenic neuroblastoma cell line (neuro2a) and subsequently injected with CpG-ODNs in the vicinity of the tumor. Daily injections of 10 microg CpG-ODNs for 15 days seemed to be the most potent regimen, leading to the eradication of 5-mm-diameter tumors in one-half of the animals and a significant tumor growth inhibition when compared with controls (88% reduction volume; $P<0.001$). CpG-ODN-cured animals were further protected against a new tumor challenge. The antitumoral effect of CpG-ODNs was dependent on CpG motifs, and natural killer cells seemed to play a critical role in tumor rejection. We conclude that immunostimulatory CpG-ODNs may induce the rejection of established tumors and warrant further evaluation as a potential immunotherapeutic agent.

PMID: 10554011 [PubMed - indexed for MEDLINE]

1: Clin Lymphoma. 2000 Jun;1(1):57-61.

CpG oligodeoxynucleotides enhance monoclonal antibody therapy of a murine lymphoma.

Warren TL, Dahle CE, Weiner GJ.

Department of Internal Medicine, University of Iowa Cancer Center, Iowa City 52242, IA, USA.

Bacterial DNA and synthetic oligodeoxynucleotides containing unmethylated cytosine-guanine dinucleotides known as cytosine phosphorothioate guanine oligodeoxynucleotides (CpG ODN) can activate various immune-cell subsets, including cells that participate in antibody-dependent cell-mediated cytotoxicity (ADCC). Studies have shown that CpG ODN enhance the efficacy of antitumor monoclonal antibody (MoAb) therapy in the 38C13 murine B-cell lymphoma. We performed a series of in vivo experiments using this tumor model to better characterize combination therapy with MoAb and CpG ODN. CpG ODN enhanced the efficacy of MoAb therapy of lymphoma in a dose-dependent manner. This effect was seen whether the CpG ODN was given before or after the MoAb therapy, but was decreased when CpG ODN was given more than 2 days after MoAb therapy. Three doses of CpG ODN and MoAb were more effective than single doses. There was no obvious toxicity with multiple dosing. These studies confirm that immunostimulatory CpG ODN enhance the efficacy of MoAb therapy, and that multiple courses of combination therapy with CpG ODN can serve as an effective therapy for lymphoma. Further exploration of this potentially potent combination of treatments, including clinical evaluation, is indicated.

PMID: 11707814 [PubMed - indexed for MEDLINE]

1: Blood. 2001 Aug 15;98(4):1217-25.

Synthetic unmethylated cytosine-phosphate-guanosine oligodeoxynucleotides are potent stimulators of antileukemia responses in naive and bone marrow transplant recipients.

Blazar BR, Krieg AM, Taylor PA.

University of Minnesota Cancer Center, Minneapolis, MN, USA.

Immunostimulatory cytosine-phophate-guanosine (CpG)--containing motifs in bacterial DNA are potent immune system activators. Depending on the bases flanking the CpG motif and on the DNA backbone, CpG oligodeoxynucleotides (ODNs) can induce relatively more B-cell activation or relatively more natural killer (NK)--cell activation. To evaluate their antitumor activities, an NK-optimized ODN (1585) and 2 B-cell--optimized ODNs (1826 and 2006) were compared for their ability to protect naive mice against a lethal acute myelogenous leukemia (AML) challenge. CpG 2006, but not CpG 1585, administered 2 days before the AML challenge, allowed mice to survive more than 100 times a lethal tumor dose. Cell depletion studies showed that protection did not require T or B cells but depended on NK cells and also on an NK-independent mechanism. CpG 2006 protected against AML challenge in both syngeneic and allogeneic bone marrow transplant (BMT) recipients at both early and late time points after transplantation. Although CpG 1585 had no protective effect on its own, it showed a striking synergy with CpG 2006 to induce prolonged survival to AML challenge in allogeneic recipients of T-cell-depleted marrow grafts, exceeding the survival benefit of donor lymphocyte infusion (DLI). When combined with DLI, a synergistic effect was observed in recipients of CpG2006 or 2006 + 1585 with 88% of mice surviving long-term. These data are the first to indicate that the systemic administration of CpG ODNs is a potent means of inducing therapeutic anti-AML innate immune responses in naive and BMT recipients. (Blood. 2001;98:1217-1225)

PMID: 11493473 [PubMed - indexed for MEDLINE]

1: Clin Cancer Res. 2001 Nov;7(11):3540-3.

Implication of macrophages in tumor rejection induced by CpG-oligodeoxynucleotides without antigen.

Auf G, Carpentier AF, Chen L, Le Clanche C, Delattre JY.

Federation de neurologie Mazarin and Institut National de la Sante et de la Recherche Medicale U-495, Hopital de la Salpetriere, 47 boulevard de l'hopital, 75013 Paris, France.

Phosphorothioate oligodeoxynucleotides containing CpG motifs (CpG-ODNs) display broad immunostimulating activity and have potential applications in cancer immunotherapy. To investigate the antitumor activity of CpG-ODNs and to study the role of macrophages and lymphocytes in tumor rejection, CpG-ODN's effects on 9 L glioma cells were assessed in Fisher rats, depleted or not in macrophages, in nude mice, and in SCID mice. In nondepleted rats, intratumoral injections with 100 microg of CpG-ODNs on days 5, 12, and 19, after s.c. 9 L cell inoculations, resulted in an 84% reduction of the tumor volumes, when compared with controls injected with saline ($P < 0.0001$). Whereas all control animals developed tumors, more than one-third of the treated rats remained tumor free. Rejection of established glioma induced a specific long-term immunity, as cured rats were protected against a subsequent 9 L injection, but not a RG2 cell inoculation, another syngenic glioma in Fischer rats. Macrophages played a critical role in the early phase of tumor rejection, because the CpG-ODN's effects were significantly decreased in the rats depleted in macrophages, and none of the macrophage-depleted rats treated with CpG-ODNs rejected the tumor. On the contrary, both nude and SCID mice, which have normal innate immunity, showed a significant decrease of tumor volume when treated with CpG-ODNs when compared with controls. T cells were however involved in a later phase of the tumor rejection, as all nude mice eventually developed tumors despite the initial tumor growth inhibition. Altogether, these data suggest that immunostimulatory CpG-ODNs induced tumor rejections through an early activation of innate immunity and priming of a specific immune response against glioma cells.

PMID: 11705874 [PubMed - indexed for MEDLINE]

1: J Immunol. 2002 Jun 15;168(12):6099-105.

Vaccination with tumor peptide in CpG adjuvant protects via IFN-gamma-dependent CD4 cell immunity.

Stern BV, Boehm BO, Tary-Lehmann M.

Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, OH 44106. Section of Endocrinology, University Hospitals, Ulm, Germany.

The low frequency of tumor Ag-specific T cells in vivo has made it challenging to directly measure their clonal sizes and cytokine signatures. We used a new generation ELISPOT approach to study the constitutive immunogenicity of the RMA tumor in syngeneic B6 mice and adjuvant-guided immunity against an MHC class II-restricted RMA peptide, H11.1. The RMA tumor was found to activate cells of the innate immune system and to induce a type 1 polarized, RMA-specific CD4 and CD8 T cell response. With clonal sizes approximately 10/10(6), the magnitude of this constitutively induced immune response did not suffice to control the tumor cell growth. In contrast, immunization with H11.1 peptide, using an immunostimulatory CpG oligonucleotide or CFA as adjuvant, engaged approximately 25- or approximately 10-fold higher clonal sizes of type 1 polarized CD4 cells, respectively. Therefore, the CpG oligonucleotide functioned as a stronger type 1 adjuvant and, unlike CFA, elicited protective immunity. The protection was IFN-gamma dependent, as it was not inducible in IFN-gamma knockout mice. Therefore, CpG adjuvant-guided induction of type 1 immunity against tumor Ags might be a promising subunit vaccination approach.

PMID: 12055220 [PubMed - indexed for MEDLINE]

Directing the Immune System to Restore Human Health

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group Initiates Phase I/II Clinical Trials of CpG 7909 for Cancer
-- U.S., European Studies to Establish Clinical Proof-of-Concept in Humans--

Wellesley, MA, USA and Hilden, Germany, - April 17, 2000

Coley Pharmaceutical Group, Inc. (CPG) has initiated the first of three Phase I/II trials of CpG DNA-based immune stimulants for the treatment of cancer, the Company announced today. The initial study, being conducted at the University of Iowa Cancer Center, is designed to evaluate the safety and immune activation of CpG DNA-based products in patients with relapsed or refractory non-Hodgkin's lymphoma. The Company's two additional Phase I/II trials in cancer will begin later this quarter in Europe.

"The rapid initiation of these three clinical trials, our first studies of CpG 7909 in cancer patients, demonstrates our commitment to our internal therapeutic focus on cancer," said Robert L. Bratzler, Ph.D., President and CEO of Coley Pharmaceutical Group. "Based on promising preclinical data, we believe that CpG DNA-based products offer an important new approach to harnessing the body's natural immune response to fight cancer. These trials provide us with our first opportunity to evaluate safety and preliminary clinical efficacy of CpG 7909, one of our lead products, for the treatment of cancer in humans." Dr. Bratzler noted that the Company currently has four additional clinical trials ongoing in infectious disease indications and in healthy volunteers, and plans to initiate Phase II clinical trials in asthma and allergy patients within the current quarter.

"Preclinical studies have demonstrated CpG DNA's ability to stimulate potent immune responses by strongly activating natural killer and cytotoxic T cells, both of which are critical for destroying tumors," said Ralph Venhaus, M.D., Vice President of Medical Affairs of Coley Pharmaceutical Group. "These Phase I/II studies allow CPG to establish clinical proof-of-concept in humans for cancer treatment, building on the knowledge that synthetic mimics of bacterial DNA fragments can be used as key therapeutic agents. Additionally, these trials are designed to evaluate multiple routes of administering CpG DNA, allowing us to understand better the potential therapeutic effects of CpG DNA-based products in cancer patients."

The Phase I/II study at the University of Iowa will involve 24 patients with refractory or relapsed non-Hodgkin's lymphoma. Primary endpoints for the trial include establishing safety and tolerability in humans. Patients in the study will receive weekly infusions of CpG 7909 for three weeks. Two additional clinical trials are being initiated in Europe: one using a CpG DNA-based cancer vaccine in melanoma patients, and one using CpG 7909 as a potential stand-alone approach for solid tumor destruction in patients with metastatic melanoma or basal cell carcinoma. CpG 7909 will be administered by intravenous, intradermal and direct tumor injection routes in the respective trials.

CpG DNA is a broadly enabling family of molecules for naturally activating the human immune system to fight disease. Coley Pharmaceutical Group's three lead products, CpG 7909, CpG 8916 and CpG 8954, consist of proprietary synthetic DNA sequences that induce distinctly different immune responses. These products provide potent anticancer and anti-infective activity when used alone or in combination with disease-associated antigens, monoclonal antibodies or traditional drug therapies. In addition, CpG DNA-based products can also "restore" allergic and asthmatic responses to more normal responses. These fundamental discoveries in DNA-based immune stimulation are protected by CPG's extensive patent portfolio.

Coley Pharmaceutical Group is a privately held biotechnology company developing innovative therapeutic and prophylactic products that harness the immune system to treat cancer, allergy, asthma and infectious diseases, and to accelerate recovery of immune system function after cancer chemotherapies or other immunosuppressive treatments. Coley Pharmaceutical Group was founded in 1997 and is headquartered in

Wellesley, Massachusetts, USA, with additional operations based in Hilden, Germany; Iowa City, Iowa, USA; Ottawa, Canada; and Osaka, Japan. Current investors include Techno Venture Management, Alafi Capital and QIAGEN N.V. (Nasdaq: QGENF).

For information contact:

Robert L. Bratzler, Ph.D.
President and CEO
Coley Pharmaceutical Group
1.781.431.6400
mail@coleypharma.com or

Sharon Karlsberg or

Wendy Soutsos
Feinstein Kean Healthcare
1.617. 577.8110
skarlsberg@fkhealth.com

Directing the Immune System to Restore Human Health

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group Begins Phase I/II Trial of CpG 7909 in Combination with Herceptin® to Treat Breast Cancer

First clinical study to evaluate ability of CpG immunomodulators to enhance monoclonal antibody treatments for cancer

Wellesley, MA, USA and Langenfeld, Germany - October 30, 2001

Coley Pharmaceutical Group, Inc., today announced that it has initiated a Phase I/II clinical trial of its lead product, CpG 7909, in multi-drug therapy with Herceptin®, Genentech's approved monoclonal antibody product. The Phase I study will determine the safety and tolerability of the multi-drug therapy in patients with refractory metastatic breast cancer. Enrollment will be limited to patients whose disease has progressed despite previous treatment with Herceptin and chemotherapy.

The objective of the trial is to determine a safe dose of CpG 7909 that may be administered with standard doses of Herceptin. Once this is established, the study will proceed with a Phase II trial for a preliminary evaluation of clinical activity of the multi-drug therapy.

"Most physicians today employ a number of different cancer therapies to achieve optimal disease treatment for their patients," stated Harold Burstein, M.D., Ph.D., of the Dana-Farber Cancer Institute and Principal Investigator of the study. "Preclinical studies have demonstrated that CpG 7909 works synergistically with monoclonal antibodies to mediate antibody dependent tumor destruction, providing early evidence to support the promise of this novel approach. I look forward to this opportunity to evaluate a potential new multi-drug therapy regimen, CpG 7909 together with Herceptin, to fight breast cancer in patients who have not responded to existing treatments."

The Phase I study will evaluate the safety and tolerability of CpG 7909 administered once weekly, 30 minutes post Herceptin infusion (per dosing instructions), in 12 to 24 patients. Patients will be distributed among up to four groups receiving CpG 7909 in a dose escalation plan to assess the maximum tolerated dose (MTD). The MTD group will be expanded to 15 patients during the Phase II study to evaluate preliminary clinical effects. If investigators observe one or more positive clinical responses, 25 additional patients will be enrolled for a total of 40, in the Phase II part of the study.

Dr. Burstein serves as the Principle Investigator for the Phase I/II study being conducted at seven clinical research centers in the U.S., including the Dana-Farber Cancer Institute. Charles Vogel, P.A.C.P., P.A., a Clinical Professor at the University of Miami School of Medicine and Hyman Muss, M.D., of Fletcher Allen Health Care in Burlington, Vermont, have also agreed to participate in the study.

"This study will be the first evaluation in patients of CpG 7909 as part of a multi-drug therapy with monoclonal antibodies," stated Robert L. Bratzler, Ph.D., President and Chief Executive Officer of Coley Pharmaceutical Group. "This initiation of our fifth clinical trial in cancer underscores our commitment to advancing our internal oncology therapeutic pipeline."

Coley's CpG immunomodulators consist of proprietary synthetic oligonucleotide sequences that induce different immune response profiles, providing the potential to target specific diseases. CpG 7909, Coley's lead product, has previously been studied in animal models as part of a multi-drug regimen with anti-cancer monoclonal antibodies. These preclinical studies showed that the addition of CpG 7909 significantly enhanced efficacy in comparison to treatment with monoclonal antibody alone. The addition of CpG 7909 is thought to improve the therapeutic effect of monoclonal antibodies by:

· Upregulating the expression of surface antigens on tumor cells to make tumors more "visible" to the immune system

· Activating the body's natural killer cells' receptors to increase their ability to target the tumor

· Increasing the recruitment of antibodies and natural killer cells to facilitate tumor destruction

Coley is also conducting clinical trials of CpG 7909 as a monotherapy for non-Hodgkin's lymphoma, basal cell carcinoma and melanoma.

About Coley Pharmaceutical Group

Coley Pharmaceutical Group discovers, develops and commercializes a new class of drugs with broad applications in cancer, asthma, allergy and infectious diseases. These proprietary products, based on CpG molecules, activate the human immune system to fight disease. Coley currently has Phase I and Phase II clinical trials ongoing, and has established a novel Human Cell Screening discovery platform for the rapid validation of new product candidates. Coley's patent portfolio includes 50 U.S. patents and patent applications, and their foreign counterparts, of which 7 have issued. Coley is a private company with operations in the United States, Germany and Canada.

For information contact:

Patricia F. Dimond, Ph.D.
Vice President, Corporate Communications, Strategic Development
Coley Pharmaceutical Group
1.781.431.6400 x1257
pdimond@coleypharma.com

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group Announces Positive Results from Ongoing Phase I Clinical Study of CpG 7909 Oligo
-- Preliminary safety and immunostimulatory activity data presented at American Society of Hematology Meeting --

Wellesley, MA - December 10, 2001

Coley Pharmaceutical Group today announced Phase I study results of the company's lead product for cancer treatment. Investigators described data on CpG 7909, an immunostimulatory oligonucleotide tested in patients with relapsed or refractory non-Hodgkins lymphoma (NHL), in a presentation today at the 43rd Annual Meeting of the American Society of Hematology. The clinical results, presented by Coley's collaborators from the University of Iowa and the University of Minnesota, show that CpG 7909 infusions were well tolerated and produced positive stimulation of the immunological responses measured in the study.

"Treating relapsed or refractory non-Hodgkins lymphoma patients remains a challenge to clinicians, despite recent advances in immunotherapy with monoclonal antibodies," said, Brian Link, M.D., Assistant Professor, Internal Medicine, at the University of Iowa College of Medicine, the study's principle investigator. "CpG 7909's side effect profile and immunomodulatory effects in this group of patients, in whom other treatment options had failed, support its safety and provides early indication of its potential to stimulate immunity."

Study Details

This Phase I study evaluated the safety, tolerability, preliminary immune stimulation and clinical effects of CpG 7909 at escalating doses as a stand-alone treatment in 16 patients with NHL. The goal of the study was to determine the Maximum Tolerated Dose (MTD) that could be safely administered to cancer patients. Patients were assigned to one of six study groups and received three weekly, two-hour infusions of CpG 7909 at doses ranging from 0.01 to 0.64 mg/kg. For purposes of the presentation at the ASH meeting, safety data were released for the first 4 groups (up to 0.16 mg/kg) and immunological data for the first 5 groups (up to 0.32 mg/kg).

CpG 7909 showed positive immunostimulatory effects that increased with higher doses, including the following:

- Increase in the primary measurement of antibody-dependent cell-mediated cytotoxicity at dose level four
- Increase in median natural killer (NK) cell activity at dose level four
- Trend towards increased numbers of NK cells

Two subjects demonstrated radiographically confirmed partial responses three months after the study ended, without having received further lymphoma treatment. All patients tolerated the weekly CpG 7909 infusion regimen well. Coley will continue this Phase I study and anticipates beginning clinical trials evaluating the safety of CpG 7909 in combination with Rituxan® shortly.

"We are extremely pleased that these early data from our first investigation of CpG 7909 in patients with non-Hodgkin's lymphoma indicate that our drug candidate has immunostimulatory effects in these patients," stated Robert L. Bratzler, Ph.D., President and Chief Executive Officer of Coley Pharmaceutical Group. "We plan to initiate a Phase I study using CpG 7909 in conjunction with Rituxan, IDEC's approved monoclonal antibody treatment for lymphoma in the near future. We anticipate the results reported today in lymphoma patients to be the first of a number of key announcements as we continue the forward momentum of our

clinical trials in multiple cancers."

About CpG Oligonucleotides

CpG oligonucleotides comprise a novel class of molecules that activate the human immune system to fight disease. Coley's product platform consists of proprietary synthetic oligonucleotide sequences that have been optimized to treat specific diseases. In addition to the NHL trial, Coley is also evaluating CpG 7909 in melanoma, and in combination with Herceptin®, Genentech's approved monoclonal antibody product, to treat refractory breast cancer.

About Coley Pharmaceutical Group

Coley Pharmaceutical Group discovers, develops and commercializes a new class of drugs with broad applications in cancer, asthma, allergy and infectious diseases. These proprietary products, based on CpG molecules, activate the human immune system to fight disease. Coley currently has Phase I and Phase II clinical trials ongoing, and has established a novel Human Cell Screening discovery platform for the rapid validation of new product candidates. Coley's patent portfolio includes 50 U.S. patents and patent applications, and their foreign counterparts, of which 7 have issued. Coley is a private company with operations in the United States, Germany and Canada. For further information, please visit www.coleypharma.com.

Directing the Immune System to Restore Human Health

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group Initiates Phase I Clinical Trial of CpG 7909 In Combination With Rituxan® to Treat Non-Hodgkin's Lymphoma

Wellesley, MA, USA and Langenfeld, Germany, - March 27, 2002

Coley Pharmaceutical Group, Inc. announced today that it has initiated a multi-center, Phase I clinical study of its lead product candidate, CpG 7909, in combination with Rituxan®, an approved monoclonal antibody product. This dose escalation study will assess the safety and tolerability of CpG 7909 in combination with Rituxan in patients with relapsed or refractory non-Hodgkin's lymphoma.

"This trial represents the second clinical investigation of our lead product candidate in combination with a monoclonal antibody. Together with our trials evaluating CpG 7909 as a monotherapy, this expanding program demonstrates our commitment to rapidly advance our clinical studies in cancer," said Robert L. Bratzler, Ph.D., President and CEO of Coley Pharmaceutical Group.

This Phase I study is the initial evaluation of CpG 7909 administered in combination with Rituxan. Participating clinical centers initiated to date include New York Presbyterian/Cornell Medical Center, New York, NY, Montefiore Medical Center, Bronx, NY and Scripps Clinic, LaJolla, CA. Patients enrolled in the study will receive four weekly intravenous infusions of Rituxan followed either by a two-hour infusion of CpG 7909 at doses ranging from 0.04 mg/kg to 0.48 mg/kg or by a subcutaneous injection of CpG 7909 at doses ranging from 0.01 mg/kg to 0.16 mg/kg. Tumor response will be measured as a secondary endpoint. Coley announced earlier its preliminary results from a Phase I clinical trial testing CpG 7909 administered alone to relapsed non-Hodgkin's B-cell lymphoma patients. In that study, CpG 7909 was well tolerated when administered intravenously and produced stimulation of the measured immune responses. Two patients showed radiographically confirmed tumor shrinkage three months after the study, and these partial responses are sustained without further lymphoma therapy.

About Coley's CpG Product Candidates

Coley's CpG product candidates consist of proprietary synthetic oligonucleotide sequences that activate different immunologic functions, allowing customized therapies for specific diseases. CpG 7909, Coley's lead product candidate, has been studied in disease models as part of multi-drug regimens in combination with anti-cancer monoclonal antibodies. Coley is also conducting clinical trials of CpG 7909 as monotherapy for non-Hodgkin's B-cell lymphoma, renal cell carcinoma and melanoma.

About Coley

Coley Pharmaceutical Group discovers, develops and commercializes a new class of drugs with broad applications in cancer, asthma, allergy and infectious diseases. These proprietary product candidates, based on CpG molecules, activate the human immune system to fight disease. Coley currently has multiple Phase I and Phase II clinical trials ongoing, and has established a novel Human Cell Screening discovery process to rapidly validate new product candidates. Coley is a private company with operations in the United States, Germany and Canada. For further information, please visit www.coleypharma.com.

Directing the Immune System to Restore Human Health

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group Initiates Phase I/II Clinical Trial of CpG 7909 for Renal Cell Cancer in U.S.A.

Wellesley, MA, U.S.A. and Langenfeld, Germany - April 30, 2002

Coley Pharmaceutical Group, Inc. announced today that it has initiated a multi-center open label, Phase I/II clinical trial of its lead product candidate, CpG 7909, for the treatment of patients with Stage IV (metastatic) renal cell carcinoma. The Phase I study will assess the safety and tolerability of escalating doses of CpG 7909. Once these are established, a Phase II group of patients will be enrolled to determine overall tumor response and immunologic effects. Other endpoints of the Phase II portion of the study include time to disease progression, duration of response and survival time.

"Because our CpG 7909 product candidate stimulates multiple aspects of immunity believed to impact tumor shrinkage, such as production of Interferon-alphas (IFN-α), Interleukin-2 (IL-2) and enhancement of natural killer cell activity, we are evaluating CpG 7909 in the treatment of this fatal cancer," said Robert L. Bratzler, Ph.D., Coley's President and Chief Executive Officer.

Study Design

In the Phase I trial, three to six patients will be enrolled at dose levels ranging from 0.08 mg/kg to 0.16 mg/kg. All patients will receive weekly subcutaneous injections of CpG 7909 for a total of 24 weeks. This phase of the trial is designed to determine the optimal treatment dosage for the Phase II portion of the study. Once the Phase I segment of the study is completed, the Phase II trial will initially enroll 12 patients treated weekly for 24 weeks with the dose previously determined in the dose escalation portion of the study. Based on the number and quality of responses in the 12 patients, 25 additional patients may be enrolled. Six centers will participate in the study in the US, including the Cleveland Clinic Cancer Center, Cleveland, Ohio; Northwestern Memorial Hospital, Chicago, Illinois; Seattle Cancer Care Alliance, Seattle, Washington; the Providence Portland Medical Center, Portland, Oregon; and Winter Park Urology Associates, Orlando, Florida.

"Clear cell carcinoma of the kidney is the most common renal malignancy and currently available treatment options are inadequate," said Ronald M. Bukowski, M.D., Director of Experimental Therapeutics at the Cleveland Clinic and the study's Principal Investigator. CPG 7909 is a novel drug, and based on very interesting preclinical data, we will evaluate its anti-tumor activity in patients with this disease."

About Coley Pharmaceutical Group

Coley Pharmaceutical Group is developing a new class of drugs with broad potential applications in cancer, asthma, allergy and infectious diseases. These proprietary product candidates, based on CpG oligonucleotides, activate the human immune system to fight disease. Coley currently has Phase I and Phase II clinical trials ongoing, and has established a novel Human Cell Screening (HCS) drug discovery and development platform for the rapid validation and optimization of new product candidates. Coley¡¦s patent portfolio includes 55 US patents and patent applications and their worldwide counterparts, including 8 US patents that have been issued. Coley is a private company with operations in the United States, Germany and Canada. For further information, please visit www.coleypharma.com.

Printable Version

Home | Site Map | Contact Us Search

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group Initiates Phase I/II Clinical Trial of CpG 7909 in Melanoma Patients

Wellesley, MA, U.S.A. and Langenfeld, Germany, - June 13, 2002

Coley Pharmaceutical Group, Inc. announced today that it has initiated a Phase I/II clinical trial of its lead product candidate, CpG 7909, as a monotherapy for the treatment of patients with Stage IV (metastatic) melanoma. The multi-center study will evaluate the safety and tolerability of weekly doses of CpG 7909, as well as overall tumor response rate in an initial study group. Based on tumor responses in this group, additional patients will be enrolled to assess the efficacy of CpG 7909 treatment.

"This trial is part of our two-pronged strategy to test CpG 7909 both as a monotherapy for treatment of cancers and as part of multidrug regimens, as in our ongoing trials of CpG 7909 with Herceptin® for breast cancer and with Rituxan® for non-Hodgkin's lymphoma," stated Robert L. Bratzler, Ph.D., President and Chief Executive Officer of Coley Pharmaceutical Group. "Because of our promising pre-clinical data and the fact that other immunological therapies, such as interferon alpha immunotherapy, have shown some, if limited, efficacy in treating melanoma, we believe that our immunostimulatory CpG 7909 may prove useful in the treatment of this intractable disease."

"The therapeutic options for metastatic melanoma, such as chemotherapy and/or non-specific immunotherapy, are rather limited and very unsatisfactory," explained Stephan N. Wagner, Ph.D., M.D., of the University Clinic for Dermatology, General Hospital of the City of Vienna, and the study's Principal Investigator. "Preclinical studies have shown that CpG 7909 alone promotes NK cell and Th1-biased T cell responses against cancer cells, including malignant melanoma, providing a scientific rationale for use of this novel immunostimulatory therapeutic strategy. I am looking forward to the opportunity to evaluate this novel drug for its anti-tumor activity in melanoma patients." The General Hospital of the city of Vienna is one of the six European Union clinical sites participating in this study.

About Stage IV (metastatic) Melanoma
Malignant melanoma is the most serious form of skin cancer. While it accounts for only four percent of skin cancers it is responsible for 79 percent of skin cancer deaths. According to the American Cancer Society, the lifetime risk of developing melanoma dramatically increased from 1 in 1,500 in 1930 to 1 in 75 in 2000. Recent projections from the National Cancer Institute estimate that 53,500 new cases of melanoma will be diagnosed in 2002, and 7,400 deaths will result from the disease. Despite current treatment options for Stage IV melanoma, which include surgery, radiation, bone-marrow transplants, single-agent and combination chemotherapy, biologic or immunotherapy therapy with interleukin or interferon, this form of cancer remains fatal for most patients.

About Coley Pharmaceutical Group
Coley Pharmaceutical Group is developing a new class of drugs with broad potential applications in cancer, asthma, allergy and infectious diseases. These proprietary product candidates, based on CpG oligonucleotides, activate the human immune system to fight disease. Coley currently has Phase I and Phase II clinical trials ongoing, and has established a novel Human Cell Screening (HCS) drug discovery and development platform for the rapid validation and optimization of new product candidates. Coley's patent portfolio includes 55 US patents and patent applications and their worldwide counterparts, including 8 US patents that have been issued. Coley is a private company with operations in the United States, Germany and Canada. For further information, please visit www.coleypharma.com.

Printable Version

Home | Site Map | Contact Us Search

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group and GlaxoSmithKline Enter Into License Agreement For Development of Cancer Vaccines

Companies to Develop Vaccines Containing CpG Immunostimulants

Rixensart, Belgium, Wellesley, MA, USA and Langenfeld, Germany - November 18, 2002

Coley Pharmaceutical Group and GlaxoSmithKline (NYSE:GSK) announced today that the companies have entered into a license agreement for the development of prophylactic and therapeutic cancer vaccines combining Coley's CpG immunostimulatory oligonucleotides and GlaxoSmithKline's cancer antigens. The agreement, the second GSK-Coley license agreement, provides GSK with a worldwide non-exclusive license to Coley's proprietary CpG immunostimulatory oligos for use as adjuvants in cancer vaccines. In exchange, Coley has received $4 MM in license issue fees and upon the achievement of certain milestones, will receive future payments, as well as license maintenance fees and royalties on products developed through the collaboration. Should cancer vaccines be successfully developed and marketed, Coley will also receive royalties on net sales of vaccines.

"We believe that Coley's CpG oligonucleotide immunostimulants will provide a significant enhancement to vaccine-induced immune responses required to treat these difficult cancers," said Jean Stéphenne, President and General Manager, GlaxoSmithKline Biologicals. "We are pleased to expand the scope our existing relationship with Coley in infectious diseases vaccines development to include the development of our anti-cancer "Pharmacine" vaccines."

"I am delighted that GSK has made CpGs an essential ingredient in their strategy to develop anti-cancer vaccines," said Robert L. Bratzler, Ph.D., President and CEO of Coley Pharmaceutical Group. "GSK is a world leader in vaccine development, and this agreement provides another validation of the potential clinical utility of our vaccine adjuvants."

About GlaxoSmithKline

GlaxoSmithKline Biologicals, the world's leading vaccine manufacturer, is located in Rixensart, Belgium. Rixensart is the centre of all GlaxoSmithKline's activities in the field of vaccine research, development and production. GSK Biologicals employs over 1,000 research scientists who are devoted to discovering new vaccines and developing more cost-effective and convenient combination products to prevent infections, which cause serious medical problems worldwide. In the year 2001 GSK Biologicals distributed over 900 million doses of vaccines to 171 countries, an average of 29 doses per second.

GlaxoSmithKline - one of the world's leading research-based pharmaceutical and healthcare companies - is committed to improving the quality of human life by enabling people to do more, feel better and live longer.

About Coley Pharmaceutical Group

Coley Pharmaceutical Group is developing several classes of immunomodulatory oligonucleotide drugs with broad potential applications in cancer, asthma, allergy and infectious diseases. The current CpG drug candidates activate the human immune system to fight disease. Coley has sixteen Phase I and Phase II clinical trials completed or ongoing with its lead product candidate, CpG 7909, a B-Class oligo. CpG 7909 is being evaluated in clinical trials as a monotherapy for melanoma and renal cell carcinoma, and in combination with Rituxan® (Mabthera®) for non-Hodgkin's B-cell lymphoma and with Herceptin® for breast cancer. Coley has established a novel Human Cell Screening drug discovery and development platform for the rapid validation and optimization of new product candidates. Coley has product development and licensing agreement with Aventis Pharmaceuticals, Inc. for the development of CpG 7279 and other products for the treatment of asthma and allergic rhinitis, as well as a licensing agreements with

GlaxoSmithKline for the use of certain CpG drug candidates in specified preventive and therapeutic infectious disease vaccines, and cancer vaccines. Coley's patent portfolio includes 65 U.S. patents and patent applications and their worldwide counterparts, including 10 U.S. patents that have been issued. Coley is a private company with operations in the United States, Germany and Canada. For further information, please visit www.coleypharma.com.

Herceptin® is a registered trademark of Genentech, Inc.
Rituxan® is a registered trademark of IDEC Pharmaceuticals.
Mabthera® is a registered trademark of F. Hoffman-LaRoche.

Printable Version

Home | Site Map | Contact Us Search

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group Announces ProMune™ (CpG 7909) Presentations at ASCO

Wellesley, MA - June 03, 2004

Coley Pharmaceutical Group, Inc. today announced that its lead product candidate, ProMune™ (CpG 7909), will be the subject of five posters at the 40th Annual Meeting of the American Society of Clinical Oncology (ASCO), June 5 - June 8, in New Orleans.

ProMune is the first of a new class of investigational synthetic agonists for Toll-like receptor 9 (TLR9) that direct the immune system to attack malignant cells, resulting in a highly selective therapy. Through TLR9, ProMune activates plasmacytoid dendritic cells and B cells, which utilize the tumor's own antigens to reverse immune tolerance to malignant cells and to drive specific, sustained anti-tumor responses with the production of antigen specific cytotoxic T cells (CTLs) and antibodies. This two-pronged immune response allows ProMune to overcome many forms of tumor resistance, and may provide immune system 'memory' against tumor recurrence.

Preclinical studies have shown ProMune to be effective in the treatment of a wide variety of both solid and hematologic tumors, both alone and in combination with cytoreductive agents, radiotherapy and monoclonal antibodies. Clinical results on ProMune in both solid and hematologic tumors will be presented at ASCO as follows:

PROMUNE FOR TREATMENT OF SOLID TUMORS

Non-Small Cell Lung Cancer: Poster Display #7126: "A TLR9 CpG Immunomodulator (ProMune™) in Combination with Chemotherapy as Treatment for Advanced Non-Small Cell Lung Cancer (NSCLC), A Randomized, Controlled Phase II Study", Gail Leichman, MD, et al., Saturday, June 5, 8:00am - 12:00pm, Lung Cancer (GP02), Board V3 Hall A (right half).

Renal Cell Carcinoma: Poster Display #4644: "Phase Ib Trial of a Targeted TLR9 CpG Immunomodulator (CpG 7909) in Advanced Renal Cell Carcinoma (RCC)," John A. Thompson, MD, et al., Sunday, June 6, 1:00pm - 5:00pm, Genitourinary Cancer (GP04), Board K10 Hall A (right half).

Melanoma: Poster Display #7513: "TLR9-Targeted CpG Immunostimulatory Treatment of Metastatic Melanoma: a Phase II Trial with CpG 7909 (ProMune™)," Stephan N. Wagner, MD, et al., Monday, June 7, 8:00am - 12:00pm, Melanoma (PD18), R02 (2nd floor, escalators 1 & 2).

Melanoma: "Melanoma Immunotherapy Discussion, Kim A. Margolin, MD, Monday, June 7, 11:00am - 11:15am, R04 (2nd floor, escalators 1 & 2).

PROMUNE FOR TREATMENT OF LYMPHOMAS

Non-Hodgkin's Lymphoma: Poster Display #6594: "Combination of CpG 7909 (ProMune™) and Rituxan® in Patients with Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma (NHL): A Phase I, Open Label Dose- Escalation Study of Safety and Tolerability", George Weiner, MD, et al., Sunday, June 6, 8:00am - 12:00pm, Hematologic Malignancies (GP16), Board K5, Hall A (right half).

Cutaneous T-Cell Lymphoma: Poster Display #6600: "Cutaneous T-Cell Lymphoma (CTCL) Responses to a TLR9 Agonist CpG Immunomodulator (CpG 7909), A Phase I Study," Youn Kim, MD, et al., Sunday, June 6, 8:00am - 12:00pm, Hematologic Malignancies (GP16), Board K11 Hall A (right

half).

ABOUT COLEY PHARMACEUTICAL GROUP
Coley Pharmaceutical Group, Inc. is an international biopharmaceutical company that discovers and develops investigational TLR Therapeutics™, a new class of drugs that direct the human immune system to treat cancers, infectious diseases, asthma and allergy. Coley has partnered programs with Aventis Pharma, GlaxoSmithKline, Chiron Corporation, and the United States Government. Coley is headquartered in Wellesley, Massachusetts, USA, and has research and development laboratories in Langenfeld, Germany, and Ottawa, Canada. For further information, please visit www.coleypharma.com.

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group Reports Initial Results of ProMune™, an Investigational Therapeutic, for the Treatment of Two Lymphomas

New Orleans, LA - June 07, 2004

Coley Pharmaceutical Group, Inc. today announced results from two Phase I clinical trials of ProMune™ (CPG 7909), the Company's lead investigational TLR Therapeutic™, in patients with recurrent or refractory lymphomas.

These open label, single arm trials were designed to evaluate the symptomatic tolerance, safety profile and pharmacokinetics of ProMune over a wide dose range of subcutaneous injections or intravenous infusions. Detailed immunologic endpoints and tumor responses were measured. Principal investigators of each study presented posters at the 40th Annual Meeting of the American Society of Clinical Oncology.

A dose escalation treatment study was carried out simultaneously in patients with the skin form of T-cell lymphoma or CTCL. Patients, who had relapsed after a mean of six prior therapies, were treated in sequentially higher dose cohorts with weekly subcutaneous injections of ProMune only and have been evaluated. Encouraging anti-tumor activity has been seen in this early phase clinical trial. Of the twenty evaluated patients, there were two complete and five partial responses beginning after four to sixteen weekly doses of ProMune. Tolerance and safety of ProMune has been encouraging and the ongoing trial continues to test optimum doses for pivotal trials.

"ProMune has significant potential in the treatment of CTCL," said Youn Kim, M.D., Associate Professor of Dermatology, Stanford University, and the lead author of the CTCL poster. "It shows activity in patients who have been previously treated with multiple other modalities, including chemotherapy and systemic biologics."

The Phase I study in Non-Hodgkin's Lymphoma enrolled fifty patients who had relapsed or refractory B-cell disease; all received four standard, weekly doses of Rituxan® plus ProMune. Initial small cohorts received sequentially higher doses of ProMune either intravenously or subcutaneously. A final cohort of 12 patients received the highest dose of 0.24 mg/kg which was then extended to a total of 24 weeks. Of the 12 patients in this cohort there were two complete responses, four partial responses, and three patients had stable disease. ProMune added no significant toxicity to Rituxan treatment.

Immune assays on patient samples from these trials confirm ProMune's activation of innate immunologic functions consistent with its known mechanism of action targeting dendritic cell activation. The most common side effects of ProMune for both clinical trials were inflammation at the injection site and flu-like symptoms; all were dose related and lasted 1 – 3 days.

"Preclinical data have demonstrated anti-lymphoma activity of CpG both as a single agent and in combination with a monoclonal antibody," said George Weiner, M.D., Professor of Medical Oncology and Director of the Holden Comprehensive Cancer Center of the University of Iowa. "Clinical data to date, while quite preliminary, are consistent with the preclinical findings, and suggest that ProMune can have a role to play in both CTCL and B-cell malignancies. Based on the toxicity profile and promising response data in these two trials, I am looking forward to future studies evaluating ProMune as a component of therapy for the hematologic malignancies."

"The clinical antitumor responses now reported in several dose escalation trials has encouraged and guided Coley's clinical development of ProMune," said John Whisnant, M.D., Senior Vice President of Drug

Development at Coley Pharmaceutical Group. "The spectrum of cancers which may benefit from ProMune includes these lymphomas and solid tumors such as metastatic melanoma and renal cancer, also reported at the ASCO meeting. Phase II, randomized trials are also being conducted to show the benefit of adding ProMune to standard chemotherapies for non-small cell lung cancer and metastatic melanoma."

About ProMune™
ProMune is the first of a new class of investigational synthetic agonists for Toll-like receptor 9 (TLR9) that direct the immune system to attack malignant cells, resulting in a highly targeted therapeutic effect. Through TLR9, ProMune activates plasmacytoid dendritic cells and B cells to reverse immune tolerance to malignant cells and to drive specific, sustained anti-tumor responses through the production of antigen-specific cytotoxic T cell lymphocytes (CTLs) and antibodies. This two-pronged immune response allows ProMune to overcome many forms of tumor resistance, and may provide immune system 'memory' against tumor recurrence.

Coley is evaluating ProMune in combination with standard chemotherapy in Phase II randomized studies for metastatic non-small cell lung cancer and melanoma. In addition, the company is extending the study evaluating ProMune in CTCL. Coley plans to initiate its first Phase III trial for ProMune in late 2004.

About Coley Pharmaceutical Group, Inc.
Coley Pharmaceutical Group, Inc. is an international biopharmaceutical company that discovers and develops investigational TLR Therapeutics™, a new class of drugs that direct the human immune system to treat cancers, infectious diseases, asthma and allergy. Coley has partnered programs with Aventis Pharma, GlaxoSmithKline, Chiron, and the United States Government. Coley is headquartered in Wellesley, Massachusetts, USA, and has research and development laboratories in Langenfeld, Germany, and Ottawa, Canada. For further information, please visit www.coleypharma.com.

PRESS RELEASE ARCHIVE

Pfizer, Coley Pharmaceutical Group Enter into Exclusive Global License for the Development and Commercialization of ProMune™ for Cancers

New York, NY and Wellesley, MA - March 24, 2005

Pfizer Inc and Coley Pharmaceutical Group, Inc. said today they have entered into an exclusive global license agreement to develop, manufacture and commercialize Coley's ProMune™ (CPG 7909), a toll-like receptor 9 (TLR9) agonist delivered by subcutaneous injection for the potential treatment, control and prevention of cancers in humans.

Under the terms of the agreement, which is subject to government approval, Pfizer will make an initial payment of $50 million to Coley, with the potential for up to $455 million in additional milestone payments, plus royalties based on the successful development and commercialization of ProMune. In addition, under certain circumstances, Pfizer will invest up to $10 million in Coley's common stock upon an initial public offering by Coley.

Pfizer will fund future development of ProMune, including planned Phase III trials for the treatment of non-small cell lung cancer. A variety of additional tumor types also will be explored. Pfizer also will fund a collaboration with Coley to discover and develop next-generation TLR9 agonists for cancers, which, if successful, could result in additional milestone payments and royalties to Coley.

"Results of clinical studies conducted to date suggest that ProMune has promising anti-cancer activity and may represent an important advance in treating a range of cancer indications," said Karen Katen, vice chairman and president, Pfizer Human Health. "This agreement is a further step in our strategy to augment Pfizer's internal research activities with externally sourced products in key therapeutic areas such as oncology, where Pfizer is working to meet the needs of cancer patients."

"We are extremely proud of our progress with ProMune, as shown in Coley's randomized Phase II clinical trials," said Robert L. Bratzler, Ph.D., Coley's President and Chief Executive Officer. "We look forward to working with the Pfizer team to realize ProMune's remarkable potential as a highly potent and broadly applicable anti-cancer therapy."

ProMune has been evaluated in clinical studies involving more than 900 subjects. Promising initial anti-cancer activity without substantial additional toxicity has been observed in both solid and hematologic tumors, both as a single agent and in combination with other treatments. The technology licensed to Pfizer by Coley includes intellectual property licensed by Coley from the University of Iowa Research Foundation in Iowa City, Iowa and the Ottawa Health Research Institute in Ottawa, Canada.

About Pfizer Inc
Pfizer Inc discovers, develops, manufactures and markets leading prescription medicines, for humans and animals, and many of the world's best-known consumer brands.

About Coley Pharmaceutical Group
Coley Pharmaceutical is an international biopharmaceutical company, headquartered in Wellesley, Massachusetts, USA, that discovers and develops TLR Therapeutics™, a new class of drugs that direct the human immune system to treat cancers, infectious diseases, asthma and allergy. The company has established a broad pipeline with four TLR Therapeutic drug candidates currently advancing through clinical development either independently or with partners, and has additional leads in early-stage development. In addition to Pfizer, Coley has partnerships with Sanofi Aventis, GlaxoSmithKline, Chiron and the United

States Government. For further information, please visit www.coleypharma.com.

#####

DISCLOSURE NOTICE: The information contained in this document is as of March 24, 2005. Pfizer assumes no obligation to update any forward-looking statements contained in this document as a result of new information or future events or developments.

This release contains forward-looking information about a product in development and the potential efficacy of such product that involves substantial risks and uncertainties. Such risks and uncertainties include, among other things, the uncertainty of the success of the research and development activities; decisions by regulatory authorities regarding whether and when to approve any new drug application for a product candidate that may result from the research, as well as their decisions regarding labeling and other matters that could affect the commercial potential of such product candidate; and competitive developments.

A further list and description of risks and uncertainties can be found in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2004, and in its reports on Form 10-Q and Form 8-K.

PRESS RELEASE ARCHIVE

Coley Pharmaceutical Group's Randomized Phase II Study Indicates that CPG 7909 has the Potential to Improve Overall Survival When Combined with Chemotherapy in First-Line Treatment of Advanced Non-Small Cell Lung Cancer

Orlando, FL - May 14, 2005

Coley Pharmaceutical Group, Inc. announced the results of a randomized Phase II study of CPG 7909 combined with standard chemotherapy in the first-line treatment of advanced non- small cell lung cancer (NSCLC). Data from the study were presented today in a poster session at the American Society for Clinical Oncology meeting.

In the study, the objective response rate was 37 percent among patients who received CPG 7909 plus chemotherapy and 19 percent in patients who received chemotherapy alone. These findings were further supported by a difference in reported median overall survival - 11.7 months for patients who received CPG 7909 plus chemotherapy and 6.8 months for patients who received chemotherapy alone. The addition of CPG 7909 was not associated with a clinically significant increase in treatment related toxicity.

"CPG 7909 represents a new class of investigational anti-cancer agents which can be combined with standard chemotherapy. CPG 7909 has the potential to improve patient outcomes in this challenging disease," said John Whisnant, M.D., Senior Vice President, Drug Development of Coley Pharmaceutical Group. "CPG 7909 is a rationally designed synthetic molecule which specifically targets Toll-like receptor 9 (TLR9) found in and on dendritic cells, resulting in immune-mediated anti-tumor responses through induction of both the innate and adaptive arms of the immune system. We believe that the results in this Phase II randomized trial are encouraging and warrant further testing in Phase III trials. We look forward to working with Pfizer as they further develop this exciting compound for the treatment of cancer."

Clinical data on 112 patients from centers in North America and Europe were presented in a poster entitled "CPG 7909, a TLR9 Agonist, Added to First Line Taxane/Platinum for Advanced Non-Small Cell Lung Cancer, a Randomized, Controlled Phase II Study," by Gail Leichman, M.D., Research Director at the Comprehensive Cancer Center at the Desert Regional Medical Center in Palm Springs, California and by Prof. Dr. Christian Manegold, of the Department of Surgery at the Heidelberg University Medical Center, Mannheim, Germany at the 2005 ASCO annual meeting, Saturday, May 14, 2005.

About the Study
Coley initiated a multi-center, randomized Phase II clinical trial in 2003 to evaluate CPG 7909 plus chemotherapy and chemotherapy alone in patients with advanced Stage IIIb or IV NSCLC. In this 112-patient clinical trial, patients were randomized 2-1 to receive 4-6 three-week cycles of a standard chemotherapy regimen of taxane/platinum alone or taxane/platinum plus subcutaneous CPG 7909 at a dose of 0.20mg/kg on weeks 2 and 3 of each 3-week cycle. The primary endpoint for the study was tumor response rate (by RECIST criteria).

Data from the study indicate that patients receiving CPG 7909 in combination with standard chemotherapy exhibited an overall response rate of 37 percent compared to 19 percent for patients receiving standard chemotherapy alone. These response data were supported by a *post-hoc* independent radiological review of CT scans that could be recovered from 91 of 112 patients. Median overall survival was 11.7 months for patients who received CPG 7909 in combination with standard chemotherapy and 6.8 months for patients who received standard chemotherapy alone. Survival follow-up remains ongoing at this time.

In keeping with earlier clinical studies of the drug, mild to moderate local injection site reactions, which were generally well tolerated and mild flu-like symptoms were the most common adverse events directly

attributable to CPG 7909.

About CPG 7909
CPG 7909 is the first of a new class of investigational medicines known as TLR Therapeutics™ being developed by Coley Pharmaceutical Group for the treatment of major medical conditions including cancer, infectious disease, allergy and asthma. TLR Therapeutics target toll-like receptors (TLRs), that act as sentinels for the body's immune system by recognizing the distinct molecular patterns characteristic of foreign pathogens. Coley is initially focusing its efforts on the discovery and development of TLR Therapeutics which stimulate TLR9.

CPG 7909 stimulates TLR9 to direct the immune system to attack malignant cells, offering the potential for a highly selective therapeutic response. Through TLR9, CPG 7909 directly and selectively activates plasmacytoid dendritic cells and B cells, which can then utilize the tumor's own antigens to fight immune tolerance to malignant cells and drive specific anti-tumor responses through the production of antigen specific cytotoxic T cells (CTLs) and antibodies.

CPG 7909 has been studied in multiple cancer indications, including both solid and hematologic malignancies, both as a single agent and in combination with various other anti-cancer therapies. In March 2005, Coley and Pfizer announced a license agreement for the development and worldwide commercialization of CPG 7909. Under the agreement, Pfizer will fund virtually all development, regulatory and commercialization costs for CPG 7909, including planned Phase III trials for the treatment of non-small cell lung cancer.

About Non-Small Cell Lung Cancer
Worldwide, lung cancer is the most commonly diagnosed cancer. In the United States, it is the leading cause of cancer deaths for both men and women. Lung cancers are comprised of two types: small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 80 percent of all lung cancer. The American Cancer Society estimates that in 2005, there will be approximately 172,000 new cases of lung cancer in the United States, and approximately 164,000 patients will die of the disease.

About Coley Pharmaceutical Group
Coley Pharmaceutical is an international biopharmaceutical company, headquartered in Wellesley, Massachusetts, USA, that discovers and develops TLR Therapeutics™, a new class of investigational drug candidates that direct the human immune system to treat cancers, infectious diseases, asthma and allergy. Coley has established a pipeline of four TLR Therapeutic product candidates currently advancing through clinical development either independently or with partners, and additional product candidates in preclinical development. Coley has product development, research and license agreements with Pfizer, sanofi-aventis, Chiron, the United States Government and GlaxoSmithKline.

Safe Harbor Statement
Certain statements in this news release concerning Coley's business are considered "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, those relating to the timing and results of future clinical development of CPG 7909 and the ability of CPG 7909 to improve tumor response and survival outcomes in patients with NSCLC and other indications. Any or all of the forward-looking statements in this press release may turn out to be wrong. They can be affected by inaccurate assumptions Coley might make or by known or unknown risks and uncertainties, including, but not limited to: the early stage of product development; uncertainties as to the future success of ongoing and planned clinical trials; and the unproven safety and efficacy of products under development. Consequently, no forward-looking statement can be guaranteed, and actual results may vary materially. Coley undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by applicable law.